Effect of intranasal administration of palivizumab on experimental respiratory syncytial viral infection - a controlled human infection study

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Study A: Validation of productive infection of RSV CHIMStudy B: Effectiveness and immunogenicity of local administration of palivizumab on prevention of experimental RSV infection

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON54420

Source
ToetsingOnline

Brief title
CHIMP

Condition

- Viral infectious disorders
- Respiratory tract infections

Synonym
bronchiolitis, RSV respiratory tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Junior Investigator Subsidie van het Longfonds

Intervention

Keyword: CHIMP, palivizumab, prevention, respiratory syncytial virus

Outcome measures

Primary outcome

Study A:

1. Productive infection (defined as 2 positive viral detections by PCR assay on

2 consecutive sampling points during the quarantine, post RSV inoculation).

Study B will start if there is productive infection in 1/6 volunteers in Study

A and there are no serious adverse events related to viral inoculation. See

detailed protocol for transition to Study B if these criteria are not met.

Study B:

1. Area under the curve (AUC) for viral load as determined by quantitative PCR

from a daily nasal-wash sample from day 2 to day 14 similar to previous studies

(Devincenzo NEJM 2014, Devincenzo NEJM 2015).

Secondary outcome

Study A: Safety measured by self-reported and physician-reported local and

systemic adverse events; transmission of RSV to healthcare workers and fomites

Study B: Safety, pharmacokinetics, lung function over time, anti-drug

antibodies, immunologic endpoints (cytokines and leukocytes)

Study description

Background summary

Globally respiratory syncytial virus (RSV) is the second cause of death after malaria in infants. RSV immunoprophylaxis with palivizumab is prohibitively expensive and only administered to high risk children in developed countries. There is a need to make palivizumab affordable through local administration. We established preclinical proof of concept in mice: intranasal (IN) palivizumab provides full protection against RSV for at least a week after administration. We tested the stability and shelf-life of a of palivizumab in nose drop formulation. In a phase I double-blind RCT we showed safety in healthy adult volunteers. This study will provide clinical proof of concept that IN administration will block RSV at the point of entry (Bouncer Hypothesis) in experimental human infection. To mitigate the risks of large and costly late-stage trials, an RSV controlled human infection model (CHIM) allows for a rapid proof of concept that is also cost-effective to test for efficacy of the proposed IN administration at an earlier stage. The World Health Organization (WHO) has determined that CHIM contributes vital scientific knowledge and can significantly accelerate clinical development.

Study objective

Study A: Validation of productive infection of RSV CHIM
Study B: Effectiveness and immunogenicity of local administration of palivizumab on prevention of experimental RSV infection

Study design

Study A: Validation of RSV CHIM in healthy adult volunteers: Productive infection in RSV CHIM; If there are 1/6 productive infections, then study B will start
Study B: Phase II RCT: Non-therapeutic double-blind placebo-controlled proof-of-concept trial of RSV prevention through IN administration of palivizumab or placebo in healthy adult volunteers

Intervention

Study A: No intervention, only viral challenge.
Study B: 0,1mL nose drops per nostril (1mg/mL palivizumab or placebo) administered one time each as a prophylaxis 2 hours before the viral challenge

Study burden and risks

This is a validation study. There are two main risks of CHIM that should be

considered (1) risk of severe infection in study subjects and (2) risk of transmission from experimentally-infected individuals to researchers or the broader public. Healthy young adults do not suffer from severe RSV infection, but at most develop mild-to-moderate common cold symptoms after experimental RSV infection. RSV CHIM has been used safely in clinical trial settings to test antivirals. The potential risk of transmission of RSV from experimentally-infected individuals to research staff and the wider public will be addressed using infection control standard procedures and will be monitored. These SOP*s will be developed and designed with the support of the Department of Infection Control at UMCU (Dr. Annet Troelstra and Dr. Herman Wunderink). The burden of the study includes 10 days of inpatient quarantine as well as minimally invasive study procedures including viral inoculation, daily nasal sampling (nasal lavage, scrape, nasopharyngeal swabs). There is no direct benefit to patients who participate in the study. Study B: This is a non-therapeutic study. The safety risks of CHIM are mitigated by evaluation of Study A to continue to Study B. The main difference is that Study B will occur in the outpatient setting. Measures will be taken to understand and carefully limit transmission risk in Study A. Furthermore, volunteers will undergo self-quarantine for a period of 10 days, be trained in transmission prevention measures as outlined above in the protocol, and will be screened for children <3 years of age in the household to limit transmission of RSV. Minimal risk is associated with the IMP which have been previously evaluated by the Ethics Committee in the Narsyn trial. Additional safety data has been collected in the phase I and IIB trial. Risks are described in more detail in section 10.4. We have shown the intranasal formulation to be safe in a phase I trial in healthy adults. The burden of the study includes 10 days of self-quarantine. Study procedures are non-invasive (nasal washes, nasosorption, lung function measurements, nasal scrapes) except for 10 blood draws. There is no direct benefit to patients who participate in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy males or females
2. Age 18-55 years
3. Signed and dated informed consent form

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: 1. Child younger than 3 years old living in subject*s household 2. Person older than 65 years old or significant primary or secondary immunodeficiency living in subjects household 3. Presence of significant acute or chronic medical illness that is associated with increased risk of respiratory viral illness related complications. These include but are not limited to: a. Recent (within adulthood) history of asthma, COPD, hypertension, reactive airway disease, or any other chronic lung illness b. History or evidence of impaired immune responsivity or autoimmune disease c. Confirmed hepatitis B (HBV), human immunodeficiency virus (HIV), or hepatitis C (HCV) test 4. Adults with a nasal cold or obstructions which could interfere with administration of the study intervention 5. Simultaneous use of other nasal drops, sprays, or medications 6. Nasal surgery prior to or during the trial 7. Positive COVID-test 48 hours prior to start of the study 8. Pregnancy 9. Symptoms of clear nasal congestion

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-08-2022
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Synagis
Generic name:	palivizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-08-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-004137-21-NL
CCMO	NL78591.041.21